

REMARKS

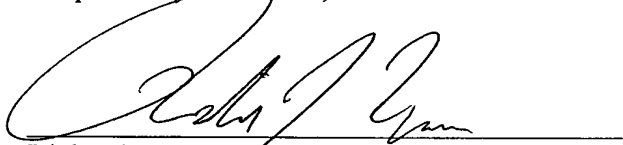
Added Claims 52 and 53 conform to cancelled composition claims 35 and 36. These claims were cancelled in response to the restriction requirement of February 8, 2001. Applicants have filed this Request for Continued Examination to obtain rejoinder of cancelled composition claims 35 and 36. Since method claims 1-34 and 37 -41 have been allowed and new claims 42-51 define subject matter which is within the scope of these allowed claims, it would not be an undue burden to examine the composition claims directed to a small number of compounds. Considering these composition claims in this application is no more burdensome than if they were presented in a continuation application.

The RCE was also filed to present additional prior art and additional claims which conform to copending application S.N. (09/640,780).

The amendments to claims 1, 3, 6, and 14 correct obvious typographical errors. The amendments to claims 28, 29, 30, and 31 serve to clarify the methods claimed. These amendments are not made for reasons of patentability. Claims 28, 29, 30, and 31 have already been found to be allowable.

New method claims 42-51 define subgeneric groups of compounds employed which are within the scope of allowed claim 1. These claims do not add new matter to the application.

Respectfully submitted,



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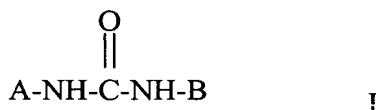
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 1, 3, 6, 14, 28, 29, 30, and 31 as follows:

1. (Amended) A method for the treatment of a disease mediated by p38 other than cancer, comprising administering a compound of formula I



wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R^{5'}, -C(O)R⁵, -NO₂, -OR⁵, -SR⁵, -NR⁵R^{5'}, -NR⁵C(O)OR^{5'}, -NR⁵C(O)R^{5'}, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₁-C₁₀ alkoxy, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₇-C₂₄ alkaryl, C₃-C₁₃ heteroaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, substituted C₁-C₁₀ alkoxy, substituted C₃-C₁₀ cycloalkyl, substituted C₄-C₂₃ alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)R⁵, -C(O)NR⁵R^{5'}, -OR⁵, -SR⁵, -NR⁵R^{5'}, -NO₂, -NR⁵C(O)R^{5'}, -NR⁵C(O)OR^{5'} and halogen up to per-halosubstitution;

wherein R⁵ and R^{5'} are independently selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₂-C₁₀ alkenyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl,

wherein Y is -O-, -S-, -N(R⁵)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁵)-, -O(CH₂)_m-, -CHX^a, -NR⁵C(O)NR⁵R^{5'}-, -NR⁵C(O)-,

$-\text{C}(\text{O})\text{NR}^5-$, $-\text{CX}^{\text{a}}_2-$, $-\text{S}-(\text{CH}_2)_m-$ and $-\text{N}(\text{R}^5)(\text{CH}_2)_m-$,

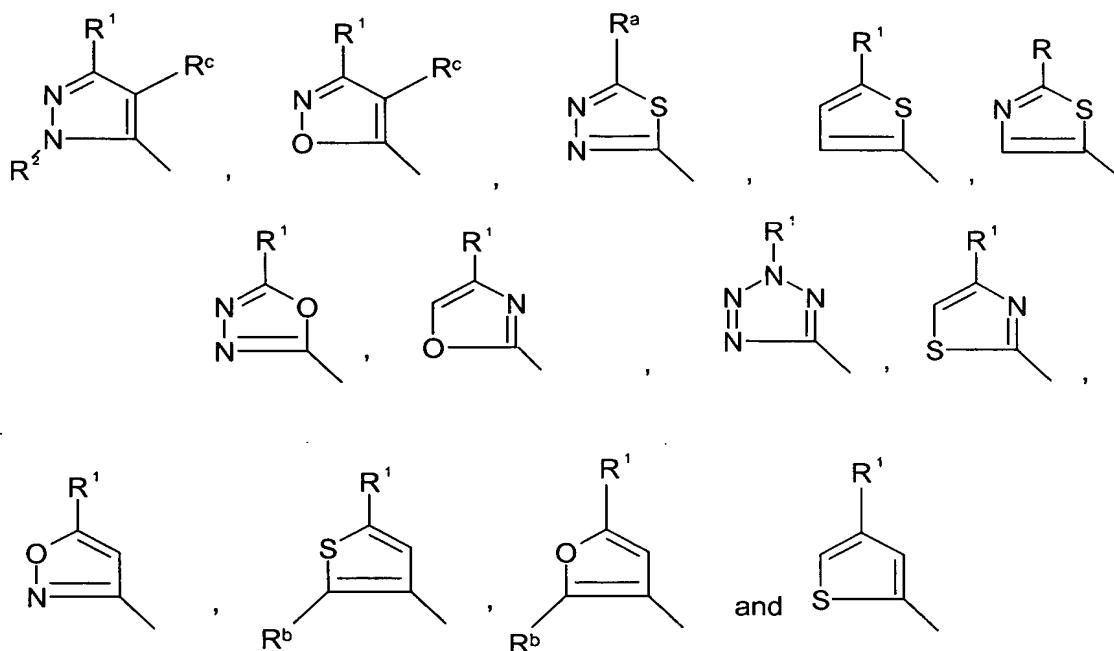
$m = 1-3$, and X^{a} is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1} ,

wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^5$, $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$, $-\text{C}(\text{O})-\text{NR}^5$, $-\text{NO}_2$, $=\text{O}$, $-\text{OR}^5$, $-\text{SR}^5$, $-\text{NR}^5\text{R}^{5'}$, $-\text{C}(\text{O})\text{R}^5$, $-\text{SO}_2\text{R}^5$, $-\text{SO}_2\text{NR}^5\text{R}^{5'}$, $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$, $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_3\text{-C}_{13}$ heteroaryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_4\text{-C}_{23}$ alkheteroaryl, substituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted $\text{C}_7\text{-C}_{24}$ alkaryl and substituted $\text{C}_4\text{-C}_{23}$ alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^5$, $-\text{C}(\text{O})\text{R}^{5'}$, $-\text{C}(\text{O})\text{NR}^5\text{R}^{5'}$, $=\text{O}$, $-\text{OR}^5$, $-\text{SR}^5$, $-\text{NO}_2$, $-\text{NR}^5\text{R}^{5'}$, $-\text{NR}^5\text{C}(\text{O})\text{R}^{5'}$, $-\text{NR}^5\text{C}(\text{O})\text{OR}^{5'}$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_4\text{-C}_{24}$ alkheteroaryl and $\text{C}_7\text{-C}_{24}$ alkaryl:-

A is a heteroaryl moiety selected from the group consisting of



wherein

R^1 is selected from the group consisting of halogen, C_3 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_1 - C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1 - C_{10} alkyl, up to per-halosubstituted C_3 - C_{10} cycloalkyl, up to per-halosubstituted C_1 - C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl;

R^2 is selected from the group consisting of H, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^3R^{3'}$, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_7 - C_{24} alkaryl, C_4 - C_{23} alkheteroaryl, substituted C_1 - C_{10} alkyl, substituted C_3 - C_{10} cycloalkyl, substituted C_7 - C_{24} alkaryl and substituted C_4 - C_{23} alkheteroaryl,

where R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^4$, $-C(O)NR^3R^{3'}$, $-NO_2$, $-OR^4$, $-SR^4$, and halogen up to per-halosubstitution,

wherein R^3 and $R^{3'}$ are independently selected from the group consisting of H, -OR⁴, -SR⁴, -NR⁴R^{4'}, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R^{4'}, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl; and

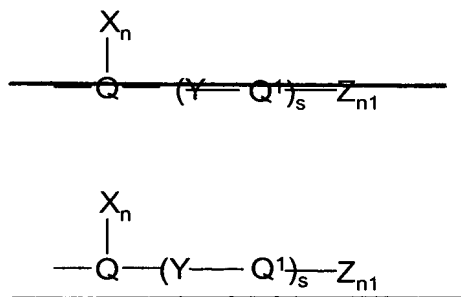
wherein R^4 and $R^{4'}$ are independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl; C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl,

R^a is C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₁-C₁₀ alkyl and up to per-halosubstituted C₃-C₁₀ cycloalkyl; and

R^b is hydrogen or halogen,

R^c is hydrogen, halogen, C₁-C₁₀ alkyl, up to per-halosubstituted C₁-C₁₀ alkyl or combines with R^1 and the ring carbon atoms to which R^1 and R^c are bound to form a 5- or 6-membered cycloalkyl, aryl or hetaryl ring with 0-2 members selected from O, N and S.

3. (Amended) A method of claim 1, wherein B is



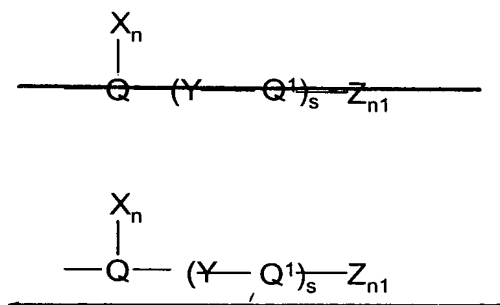
wherein Y is selected from the group consisting of -O-, -S-, -CH₂-, -SCH₂-, -CH₂S-, -CH(OH)-, -C(O)-, -CX^a₂, -CX^aH-, -CH₂O- and -OCH₂-, where X^a is halogen,

Q is a six member aromatic structure containing 0-2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution, and

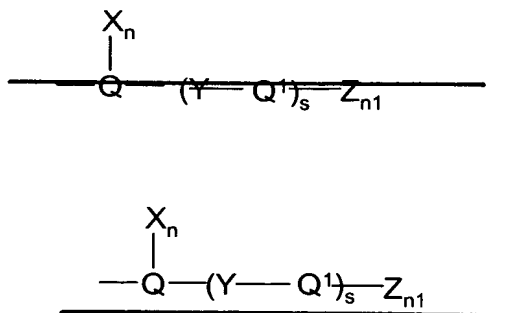
X, Z, n and n_1 are as defined in claim 1 and s is 0 or 1.

6. (Amended) A method as in claim 5, wherein B is 2,3-dichlorophenyl or of the formula



wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is -O-, -S-, -CH₂- or -SCH₂, X is CF₃, and Z is -OH, -Cl or NHC(O)-C_pH_{2p+1}, where p = 2-4, s = 0 or 1, n = 0 and n_1 = 0 or 1.

14. (Amended) A method as in claim 13, wherein B is 2,3-dichlorophenyl or of the formula



wherein Q is phenyl, Q^1 is phenyl, pyridinyl or benzothiazolyl, Y is -O-, -S-, -CH₂- or -

NH-, Z is Cl, -CH₃ or -OCH₃, s = 0 or 1, n = 0 and n1 = 0 or 1.

28. (Amended) A method as in claim 1, wherein the compound for formula I displays p38 IC₅₀'s activity (~~IC₅₀~~) ~~better~~ less than 10 μm as determined by an in-vitro p38 kinase inhibition assay.

29. (Amended) A method according to claim 1, wherein the disease is mediated by a cytokine ~~or~~ and/or protease (proteolytic enzyme) regulated by p38.

31. (Amended) A method according to claim 1 ~~+~~ 29, comprising administering an amount of a compound of formula I effective to inhibit production of a disease-mediating cytokine or protease.